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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DENISE L. FAUSTMAN

Appeal 2007-3894
Application 09/913,664
Technology Center 1600

Decided: May 30, 2008

Before TONI R. SCHEINER, ERIC GRIMES, and LORA M. GREEN, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of inhibiting transplant rejection, which the Examiner has rejected as anticipated by or obvious over the prior art. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

BACKGROUND

The Specification discloses a method for "reducing or eliminating, at least temporarily, the susceptibility of transplanted (donor) tissues to immune-mediated attack by the host's immune system" (Spec. 1). The method comprises "treating the transplanted (donor) tissue with an enzyme

capable of cleaving antigenic structures expressed on the cells of the donor tissue. The antigenic structures can be, for example, donor MHC Class I antigens. Removal of MHC Class I antigens from the donor tissue will attenuate the extent of the immune response mounted by the host mammal receiving the transplant." (*Id.* at 3-4.) "Papain is the most preferred enzyme for treatment of donor tissue for removal of MHC class I antigens" (*id.* at 4).

DISCUSSION

1. CLAIMS

Claims 1-14 and 16-23 are pending and on appeal. Claims 1 and 12, the only independent claims, read as follows:

> 1. A method for inhibiting rejection by a host mammal of donor tissue from another mammal which is transplanted into the host mammal, said method comprising
>
> (a) treating viable donor tissue with an enzyme effective for temporarily ablating MHC Class I antigens from said donor tissue,
>
> (b) transplanting said treated, viable donor tissue into said host mammal before MHC Class I antigens are re-expressed on the surface of said donor tissue, and
>
> (c) maintaining said viable donor tissue in said host.
>
> 12. A method for inhibiting rejection by a host mammal of donor tissue from another mammal which is transplanted into the host mammal, said method comprising:
>
> (a) treating a first viable donor tissue with an enzyme effective for temporarily ablating MHC Class I antigens from said donor tissue,
>
> (b) transplanting said treated, viable donor tissue into said host

> mammal before MHC Class I antigens are re-expressed on the surface of said donor tissue, and
>
> (c) maintaining said viable donor tissue in said host mammal, and
>
> (d) transplanting a second donor tissue into said host mammal.

2. ANTICIPATION

Claims 1, 2, and 5 stand rejected under 35 U.S.C. § 102(b) as anticipated by Civin.[1] The Examiner finds that Civin

> discloses a method for transplantation [of] bone marrow cells wherein the method comprises step of treating a viable donor tissue with enzyme chymopapain (col. 11, lines 30-35), step of transplanting the treated viable donor tissue into host mammal (col. 11, line 45) and step maintaining the treated viable donor tissue in the host mammal (col. 11, line 57). . . . The cited patent is considered to anticipate the claimed invention because it comprises identical active steps and, thus, the intended effects are reasonably expected to be identical as related to removal of antigens of MHC class I and to inhibition of donor tissue rejection.

(Answer 4.)

Appellant argues that the example pointed to by the Examiner is not a "method of inhibiting rejection," as recited in claim 1, because the donor and recipient rats in that example are described as syngeneic, so no rejection would occur (Reply Br. 4-5).

The preamble of claim 1 states that the method is "for inhibiting rejection by a host mammal of donor tissue from another mammal which is transplanted into the host mammal." "If the claim preamble, when read in

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[1] Civin, U.S. Patent 5,081,030, issued Jan. 14, 1992.

the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." *Pitney Bowes Inc. v. Hewlett Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999).

In this case, we agree with Appellant that the preamble language of claim 1 excludes transplant of syngeneic tissues. The only purpose of the enzyme-treatment step in the claimed method is to eliminate MHC class I antigens from the cells of the donor tissue in order to reduce the immune reaction caused by the donor tissue when transplanted into a recipient. The preamble language therefore is "necessary to give life, meaning, and vitality" to the claims, *Pitney Bowes*, 182 F.3d at 1305, and effectively limits the claimed method to one in which the recited donor tissue and host mammal are not syngeneic.

In the working example of Civin that the Examiner relies on, the bone marrow donor cells and the recipient rats are described as syngeneic (Civin, col. 11, ll. 43-45) and the cells were not rejected by the donors whether or not they were treated with chymopapain (*id.* at col. 11, ll. 56-62). We therefore agree with Appellant that Civin's Examples 10 and 11 do not show a "method for inhibiting rejection" and do not anticipate the instant claims.

Appellant also argues that Civin's broader disclosure does not anticipate the instant claims because Civin's method is intended to isolate stem cells from bone marrow and stem cells don't express MHC class I

antigen complexes on their surface (Appeal Br. 7-9). As supporting evidence, Appellant cites Itescu[2] and Gabbianelli.[3]

The Examiner responded that Itescu and Gabbianelli "relate to the *embryonic* stem cells. The Civin patent discloses the use of *adult* tissues but *not embryonic* stem cells" (Answer 10-11). The Examiner also cites Abbas[4] as evidence that MHC class I molecules are "expressed on virtually all nucleated cells [as] is a common knowledge to the person of ordinary skill in the art of immunology" (*id.* at 11).

This factual dispute is central to the issue of anticipation: if Civin's immunoaffinity-purified cells have MHC class I molecules on their cell surface (the Examiner's position), the chymopapain treatment taught by Civin would reasonably appear to "ablat[e] MHC class I antigens," as required by claim 1. If there are no MHC class I antigens to be ablated (Appellant's position), then Civin's chymopapain treatment of its purified cells does not meet the claim limitations.

We conclude that the Examiner's position is not supported by a preponderance of the evidence of record, as would be required to support a factual finding that Civin anticipates claim 1. *See In re Oetiker*, 977 F.2d

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[2] Itescu, "Stem cells and tissue regeneration: Lessons from recipients of solid organ transplantation," Appendix L in *Monitoring Stem Cell Research*, President's Council on Bioethics (2004).
[3] Gabbianelli et al., "HLA expression in hematopoietic development: Class I and II antigens are induced in the definitive erythroid lineage and differentially modulated by fetal liver cytokines," *Journal of Immunology*, Vol. 144, pp. 3354-3360 (1990).
[4] Abbas et al., *Cellular and Molecular Immunology*, 5th Edition, Saunders (2003).

1443, 1449 (Fed. Cir. 1992) ("In rejecting an application, factual determinations by the PTO must be based on a preponderance of the evidence.") (Plager, J., concurring).

Itescu states that the "Major Histocompatibility Complex (MHC) . . . encodes the alloantigens known as Human Leukocytes Antigens (HLA)" (Itescu 2). Itescu also states that "[s]tem cells obtained from embryonic or adult sources differ from other somatic cells in that they express very low levels of HLA molecules on their cell surfaces" (*id.* at 2). Civin teaches a method for isolating "normal marrow stem cells" using an antibody to the MY-10 epitope on the CD34 glycoprotein (Civin, col. 2, ll. 8-21).

Although Appellant's evidence does not state unequivocally that Civin's $CD34^+$ stem cells do not express MHC class I molecules, neither does Civin unequivocally state that they do. We find that the evidence provides a reasonable basis for doubting that Civin's disclosure inherently meets all the limitations of claim 1. Therefore, Appellant's showing shifts the burden back to the Examiner to provide evidence, of at least equal probative weight, that the disputed limitation is in fact present in Civin. *See Oetiker*, 977 F.2d at 1445 ("After evidence or argument is submitted by the applicant in response [to the prima facie case], patentability is determined on the totality of the record, by a preponderance of evidence.").

The Examiner cites Abbas' statement that "[c]lass I molecules are constitutively expressed on virtually all nucleated cells, whereas class II molecules are normally expressed on only dendritic cells, B lymphocytes, macrophages, and a few other cell types" (Abbas 78). The Examiner also

cites a statement in Galati[5] that "MHC class I molecules are . . . expressed on most nucleated cells" (Galati 77).

We conclude that the weight of the evidence of record does not support the Examiner's position that Civin's $CD34^+$ stem cells inherently express MHC class I molecules. The evidence cited by the Examiner states only that *most* nucleated cells express MHC class I molecules. The statements by Abbas and Galati are consistent with Itescu's statement that "[s]tem cells . . . differ from other somatic cells in that they express very low levels of HLA molecules" (Itescu 2). That is, the statements by Abbas and Galati may well mean that most nucleated cells, but not stem cells, express MHC class I molecules.

In rejecting a claimed invention as unpatentable, the Examiner bears the ultimate burden of persuasion. *See Oetiker*, 977 F.2d at 1449 ("[T]he examiner has the burden of persuasion and therefore the initial burden of production. . . . Once that burden is met, the applicant has the burden of production to demonstrate that the examiner's preliminary determination is not correct. The Examiner . . . retain[s] the ultimate burden of persuasion on the issue.") (Plager, J., concurring)

We conclude that the Examiner has not established, by a preponderance of the evidence, that Civin meets all the limitations of claim 1. We therefore reverse the rejection of that claim as anticipated by Civin. We also reverse the rejection of claims 2 and 5 because those claims depend on claim 1.

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[5] Galati et al., "Quantitative cytometry of MHC class I digestion from living cells," *Cytometry*, Vol. 27, pp. 77-83 (1997).

3. OBVIOUSNESS I

Claims 1-9, 12-14, and 16-23 stand rejected under 35 U.S.C. § 103 as obvious in view of Civin, Galati, Lee,[6] and Brownlee.[7] We have already concluded that the Examiner has not established that Civin's method meets all the limitations of claim 1. Claim 12, the only other independent claim, includes all the limitations of claim 1, so Civin also fails to meet all the limitations of the rest of the rejected claims. The central issue with respect to obviousness, then, is whether Galati, Lee, and Brownlee would have suggested applying Civin's method to cells that express MHC class I antigens.

The Examiner relies on Galati as evidence that papain removes MHC class I antigens from cells (Answer 6); Lee "is relied upon to demonstrate that hepatocytes and islet[] cell[] preparations intended for transplantation are prepared by enzymatic treatment with enzymes chymopapain or papain" (*id.*); and Brownlee is cited as evidence that "cells treated with papain in order to remove MHC class I surface molecules remain viable, functional and they will re-express the MHC class I surface molecules" (*id.* at 7).

Appellant argues that "the Galati, Lee, and Brownlee references do not provide a 'bridge' linking the teachings of Civin with the present invention, and therefore the citation of the references cannot support a *prima facie* case of obviousness" (Appeal Br. 13).

We agree with Appellant that the Examiner has not made out a prima facie case of obviousness. The Examiner has not provided an adequate

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[6] Lee et al., U.S. Patent 5,670,358, issued Sept. 23, 1997.
[7] Brownlee et al., U.S. Patent 6,156,306, issued Dec. 5, 2000.

explanation of what would have led those skilled in the art to apply Civin's method to cells that express MHC class I antigens.

The Examiner points to Lee's disclosure of treating hepatocytes and islet cells with papain or chymopapain (Answer 6). It is unclear, however, how the enzyme treatment of hepatocytes and islet cells described in Lee would have suggested using those cells in Civin's method: Civin's method is directed to purifying bone marrow stem cells from other bone marrow cells via immunoaffinity chromatography based on the cell-surface marker CD34. The Examiner has pointed to no evidence showing that hepatocytes or islet cells express the CD34 antigen, such that it would have been obvious to use Civin's anti-MY10 antibody to bind them to a support, and then cleave them from the support using papain or chymopapain.

The Examiner has not adequately shown that the cited references would have suggested the method defined by claims 1 and 12. We therefore reverse the rejection of those claims, and the rejection of dependent claims 2-9, 13, 14, and 16-23.

4. OBVIOUSNESS II

Claims 1-14 and 16-23 stand rejected under 35 U.S.C. § 103 as obvious in view of Civin, Galati, Lee, Brownlee, and Stone.[8] The Examiner relies on Stone only to meet the limitation of claims 10 and 11 that the donor tissue is treated with α-galactosidase (Answer 8). Stone does not make up for the deficiency of the other references, and we reverse this rejection for the reasons discussed above.

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[8] Stone et al., "Porcine cartilage transplants in the cynomolgus monkey," *Transplantation*, Vol. 65, pp. 1577-1583 (1998).

SUMMARY

The Examiner's rejections are not supported by a preponderance of the evidence of record. We therefore reverse the rejections on appeal.

REVERSED

dm

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